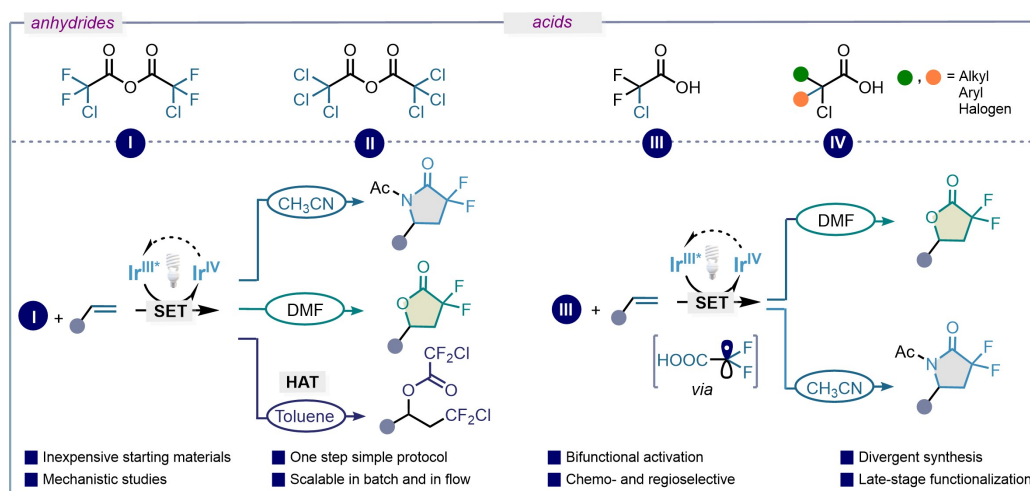


Photoredox Activation of Anhydrides and Acids for the Solvent-Controlled Switchable Synthesis of *gem*-Difluoro Compounds

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The outstanding impact of fluorine in drug discovery and development cannot be underestimated, since 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. Substantially, the incorporation of the *gem*-difluoro (CF₂) motif into organic frameworks is highly desired due to the influence of this unit on the physicochemical and pharmacological properties of molecules.^[1] However, the introduction of such synthon requires the use of prefunctionalized starting materials or a surrogate at the beginning of the synthesis. To address this limitation chlorodifluoroacetic anhydride (CDFAA, I) can be selected as promising precursor because it is an abundant source of fluorine building blocks and it possesses varied reactivity. In the context of the divergency and applicability of such reagents, switchable synthesis can be beneficial to access a wide range of fluorinated compounds. Herein we present our studies to access *gem*-difluoro compounds that employ CDFAA as a low-cost and versatile fluoroalkylating reagent. Extensive mechanistic studies revealed that electron-transfer photocatalysis triggers mesolytic cleavage of a C–Cl bond generating a *gem*-difluoro carboxy radical. In the presence of olefin, this radical species acts as unique and efficient bifunctional reagent that, under solvent-controlled reaction conditions, delivers a wide range of *gem*-difluorinated γ -lactams, γ -lactones, as well as promotes oxy-perfluoroalkylation.^[2] Due to the fact that most anhydrides are prepared from the corresponding acids, developing a mild and operationally simple strategy to access *gem*-difluoro compounds using chlorodifluoroacetic acid (CDFA, III) can serve as a beneficial entry for achieving a step-economic and practical synthesis of fluorinated scaffolds. We found, that depending on the polarity of the solvent, CDFA can exhibit varied reactivity under photoredox conditions in the presence of an alkene precursor.^[3] These methodologies are flow and batch scalable, possess excellent chemo- and regioselectivity, and are useful for late-stage diversification of complex organic scaffolds.



[1] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320–330.

[2] R. Giri, I. Mosiagin, I. Franzoni, N. Y. Nötzel, S. Patra, D. Katayev *Angew. Chem. Int. Ed.* **2022**, 61, e202209143.

[3] R. Giri, D. Katayev **2023**, *in preparation*.